Circulating tumor cell counts are prognostic of overall survival in SWOG S0421: a Phase 3 trial of docetaxel with or without atrasentan for metastatic castration resistant prostate cancer

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Supplementary Methods

Data Analysis and Statistical Considerations: The overall results of the parent S0421 trial showed no differential survival benefit for the atrasentan arm,[1] so CTC count was analyzed only as a prognostic biomarker, not as a predictive biomarker (i.e. differential response to therapy). The association of CTC count with overall survival (OS) was analyzed by Cox regression analysis. Baseline CTC counts were dichotomized at >=5 vs. < 5 based on prior work by DeBono and colleagues.[2] Changes in CTC counts after one cycle of treatment were evaluated for an association with post-cycle 1 OS in a landmark analysis defined as 3 weeks post-randomization. CTC counts were log transformed to adjust for skewed distribution. Additional models were fit for patients with low and high baseline CTC counts (≥5 vs. <5) to account for the "floor effect" in patients with <5 CTC at baseline (minimal ability of counts to drop in this group). In patients with high (≥5) baseline CTC count, a drop ≥50% in CTC counts after one cycle was also evaluated because of the inherently greater variability of CTC counts at high numbers. All models were adjusted for covariates ($\log_2$) baseline PSA, age, race (African American vs. all other), performance status, progression prior to study entry (PSA vs. radiologic), worst bone pain >= 4 via the Brief Pain Inventory,[3] presence of extraskeletal metastases (yes vs. no), presence/absence of liver disease, and relevant laboratory tests (hemoglobin, $\log_2$ alkaline phosphatase). The models for a change in CTC counts at d21 were adjusted for baseline CTC count. To evaluate the prognostic capacity of CTC counts, ROC curves and the area under the curve (AUC) were estimated for both baseline CTC counts and baseline PSA predicting 2-year OS[4], and we estimated the

integrated discrimination improvement (IDI) from adding baseline CTC counts to a Cox regression model that included baseline PSA or baseline PSA + the previously listed covariates using the method of Chamblis et al.[5] In an exploratory analysis, prognostic subgroups were identified by regression tree analysis to find the optimal cutpoint(s).[6] The same baseline characteristics listed above were candidates for this analysis. Survival was graphically displayed for each prognostic group using the methods of Kaplan and Meier. Baseline CTC counts or changes in CTC counts (d0 to d21) also were evaluated for association with PSA response (defined as 50% reduction at any time point) adjusting for other risk factors in a logistic regression model. The association of CTCs with objective confirmed and unconfirmed complete and partial response by RECIST criteria,[7] was evaluated with the chi square test.

References:

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